(3) Rejection of claim 68 under 35 USC § 103(a) as being unpatentable over Coyle et al. in view of Greenberger and Le Gal La Salle et al.;

(4) Rejection of claims 47 and 61-82 under 35 USC § 112, second paragraph.

Each of the issues raised by the Examiner are discussed in order below. Applicants believe that the foregoing amendment and the following remarks respond completely to these issues. Applicants further believe that the pending claims as amended are in condition for allowance.

(1) Rejection of claims 47, 61-65, 67 and 69-81 under 35 USC § 103(a) as being unpatentable over Coyle et al. in view of Greenberger

Claims 47, 61-65, 67 and 69-81 stand rejected under 35 USC § 103(a) as being unpatentable over Coyle et al. in view of Greenberger. Applicants traverse the rejection and submit that this combination of references in no way teaches or suggests Applicants' invention and, therefore, fails to establish a *prima facie* case of obviousness. Accordingly, Applicants request respectfully that the rejection be reconsidered and withdrawn.

(a) Discussion of the cited references

Coyle et al.

Coyle et al. discuss potential relationships between oxidative stress and/or excessive activation of glutamate receptors on the neuropathology of several neurodegenerative disorders. The reference teaches that superoxide dismutase (SOD) is one of several enzymes which neutralize oxygen radicals. Coyle et al. also teach that mice transgenic for copper/zinc SOD (CuZnSOD) are resistant to the neurotoxic activity of MPTP, a compound which induces symptoms of Parkinson's disease. The reference also teaches that mutations in CuZnSOD have been observed in families suffering from one form of amyotrophic lateral sclerosis.

Coyle et al. neither teach nor suggest a replication defective recombinant adenovirus comprising a gene encoding a SOD. Coyle et al. certainly do not teach treatment of a disease by administration of such an adenovirus to a

patient. Applicants were the first to suggest the claimed invention, and to demonstrate its efficacy.

Greenberger

Greenberger teaches a method of protecting normal cells against the toxic species of an anticancer agent or ionizing radiation by administering a polynucleotide encoding gamma glutamyl transpeptidase, superoxide dismutase or metallothionein. Delivery of a gene encoding MnSOD is exemplified in the application. The polynucleotide may be delivered by a replication defective adenovirus vector.

(b) Coyle et al. neither teach nor suggest the claimed invention

Independent claim 47 defines a method of treating a disease selected from atherosclerosis, cardiovascular disease, diabetes, retinopathy, cataract formation, Parkinson's disease, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, 21 trisomy, and hypertension, by administering to a patient a replication defective, recombinant adenovirus comprising a DNA sequence encoding a superoxide dismutase under the control of a signal enabling expression in a target cell. Coyle et al. neither teach nor suggest the invention defined by claim 47. The reference is deficient for the following reasons:

1) it fails to establish a reasonable expectation that modification of superoxide levels in a patient would be expected to benefit a patient suffering from any of the claimed disease states; and

2) it fails to teach or suggest delivery of a gene encoding SOD to a patient suffering from any disease.

Absent such a disclosure, Coyle et al. cannot possible render obvious the invention defined by claim 47, or any of the claims dependent thereon.

Coyle et al. is merely a review of the potential relationships between oxidative stress and/or excessive activation of glutamate receptors on the neuropathology of several neurodegenerative disorders. The authors

characterize the role of oxidative stress on the proximate cause of degenerative disorders as a only a "hypothesis" (page 689, first column), and conclude that

> Understanding the relation between oxidative stress and Glu neurotransmission could lead to the development of pharmacologic interventions...

(see page 689, second column, emphasis added). Clearly, Coyle et al. are merely at the stage of attempting to understand the role of oxidative stress on degenerative disease. Once this role is established the reference suggests that new drugs may someday result. Such speculation on a system characterized by the reference as only a "hypothesis" cannot stand as the basis for a *prima facie* case of obviousness. Indeed, the Examiner clearly recognizes the inherent uncertainty in Coyle et al. by stating that the authors review

> the **possible correlation** between reduction or loss (sic) of CuZnSOD activity with diseases such as ALS in humans

(Office action at page 3, emphasis added).

By contrast, Applicants' have enabled and claimed their invention directed to a method for treating a disease selected from atherosclerosis, cardiovascular disease, diabetes, retinopathy, cataract formation, Parkinson's disease, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, 21 trisomy, and hypertension by administering to a patient a replication defective, recombinant adenovirus comprising a DNA sequence encoding a superoxide dismutase. Applicants were the first to suggest the claimed invention, and to demonstrate its efficacy *in vivo*. As evidence thereof, Applicants direct the Examiner's attention to Barkats et al. 1996 and Barkats et al. 1997 (attached to the reply filed April 2, 1998 as Exhibits A and B, respectfully).

Barkats et al. teach that intrastriatal grafting of rat neurons comprising an adenovirus encoding human CuZnSOD improved behaviour in a rat model of Parkinson's disease when compared to a control adenovirus. In particular, Barkats *et al.*, 1996 demonstrate that adenoviral-mediated gene transfer of human CuZnSOD is an efficient means to produce the enzyme in neuronal cells. The authors demonstrate that the exogenous CuZnSOD enzyme is functional, and that the resultant intracellular levels of CuZnSOD are sufficient to protect neurons from glutamate-induced cell death. Barkats *et al.*, 1997 demonstrate the use of intrastriatal grafts of embryonic mesencephalic rat neuronal cells that

are infected *ex vivo* with a replication defective adenovirus encoding human CuZnSOD to treat Parkinson's disease in a rat model. The grafts exhibited sustained expression of the exogenous CuZnSOD for at least 5 weeks postgrafting and resulted in a more extensive functional recovery compared to the controls, as determined by rotational behavior. In addition, the inflammatory consequences of adenoviral gene transfer were minimal. Finally, the authors described a trend for improved graft survival after Ad-CuZnSOD infection which may be associated with the potential neuroprotective effect of intracellular overexpression of CuZnSOD. Thus, Barkats et al. demonstrate effective transfer of CuZnSOD by a replication defective recombinant adenovirus.

The efficacy of the claimed invention, as evidenced by Barkats et al., cannot be predicted from Coyle et al. Indeed, one skilled in the art could have expected an opposite result. Bar-Peled et el. (PNAS 93, 8530-8535, 1996; attached hereto as Exhibit A) teaches that overexpression of CuZnSOD can lead to chronic oxidative stress, and ultimately apoptosis of neuronal cells. Therefore, Bar-Peled et al. teaches away from the claimed invention, and corroborates the inherent unpredictability of Coyle et al., which is apparently recognized by the Examiner.

(c) Greenberger fail to remedy the deficiencies of

As stated above, Greenberger simply teaches a method of protecting normal cells against the toxicity of an anticancer agent or ionizing radiation by administering a polynucleotide which may encode a superoxide dismutase. Significantly, Greenberger does not teach a method of treating a disease selected from atherosclerosis, cardiovascular disease, diabetes, retinopathy, cataract formation, Parkinson's disease, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, 21 trisomy, and hypertension. Greenberger certainly does not teach that administration of a replication defective, recombinant adenovirus comprising a DNA sequence encoding a superoxide dismutase would effectively treat a disease as claimed. Applicants were the first to make this unexpected discovery

(d) Conclusion

Obviousness under Section 103 is a question of law. Panduit Corp. v. Dennison Mfg. Co., 1 USPQ2d 1593, 1597 (Fed. Cir.), cert denied, 481 U.S. 1052 (1987). The burden of establishing a *prima facie* case of obviousness

resides with the PTO. In re Piasecki, 223 USPQ 785, 788 (Fed. Cir. 1984) (quoting In re Warner, 154 USPQ 173, 177 (CCPA 1967)). Applicants submit respectfully that the Examiner has failed to meet this burden. Specifically, it is well established that "(b)oth the suggestion and the expectation of success must be founded in the prior art, not in Applicants' disclosure." In re Dow Chemical Company, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). The cited references fail on both accounts. In particular, nothing in the art cited by the Examiner teaches or suggests a method as claimed. It follows that these references cannot provide a reasonable expectation that the method as claimed would be effective. Indeed, the references cited by the Examiner, in addition to Bar-Peled et al., suggest otherwise. Applicants were the first to make this unexpected discovery. Accordingly, this rejection is untenable and should be withdrawn.

(2) Rejection of claims 66 and 82 under 35 USC § 103(a) as being unpatentable over Coyle et al. in view of Greenberger and Englehardt et al.

Claims 66 and 82 stand rejected under 35 USC § 103(a) as being unpatentable over Coyle et al. in view of Greenberger and Englehardt et al. Applicants traverse the rejection and submit that, for the reasons discussed above, this combination of references in no way teaches or suggests Applicants' invention and, therefore, fails to establish a *prima facie* case of obviousness.

The deficiencies of the combination of Coyle et al. with Greenberger are discussed above. Englehardt et al. fail to remedy these deficiencies. Specifically, Englehardt et al. simply teach second generation recombinant adenoviruses containing a beta-galactosidase-expressing transgene, and a temperature-sensitive mutation in the E2A gene of the virus genome.

Englehardt et al. do not teach a method of treating a disease selected from atherosclerosis, cardiovascular disease, diabetes, retinopathy, cataract formation, Parkinson's disease, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, 21 trisomy, and hypertension as claimed. Englehardt et al. certainly do not teach that administration of a replication defective, recombinant adenovirus comprising a DNA sequence encoding a superoxide dismutase would effectively treat such a disease. Applicants were the first to make this unexpected discovery. Accordingly, this rejection is untenable and should be withdrawn.

(3) Rejection of claim 68 under 35 USC § 103(a) as being unpatentable over Coyle et al. in view of Gre nberger and Le Gal La Salle et al.

Claim 68 stands rejected under 35 USC § 103(a) as being unpatentable over Coyle et al. in view of Greenberger and Le Gal La Salle et al. Applicants traverse the rejection for the reasons discussed above. In particular, this combination of references neither teaches nor suggests Applicants' invention and, therefore, fails to establish a *prima facie* case of obviousness.

Again, the deficiencies of the combination of Coyle et al. with Greenberger are discussed above. Le Gal La Salle et al. fail to remedy these deficiencies. Specifically, Le Gal La Salle et al. simply teach a recombinant adenovirus comprising the RSV-LTR promoter.

Le Gal La Salle et al. do not teach a method of treating a disease selected from atherosclerosis, cardiovascular disease, diabetes, retinopathy, cataract formation, Parkinson's disease, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, 21 trisomy, and hypertension as claimed. Le Gal La Salle et al. certainly do not teach that administration of a replication defective, recombinant adenovirus comprising a DNA sequence encoding a superoxide dismutase would effectively treat such a disease. Applicants were the first to make this unexpected discovery. Accordingly, this rejection is untenable and should be withdrawn.

(4) Rejection of claims 47 and 61-82 under 35 USC § 112, second paragraph.

Claims 47 and 61-82 stand rejected under 35 USC § 112, first paragraph as indefinite. Applicants have amended claim 47 according to the Examiner's suggestion. Accordingly, Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

In view of the foregoing amendment and remarks, Applicants request respectfully reconsideration and withdrawal of all rejections. Applicants further submit that the claims are in condition for allowance and an early notice to this effect is earnestly solicited.

If a telephone interview would be of assistance in advancing prosecution of this application, Applicants attorney invites the Examiner to contact him at the number provided below.

Dated: January 6, 1999

Respectfully submitted,

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